Accepted Manuscript

An Overview of the Risk of Lung Cancer in Relation to Exposure to Asbestos and of Taconite Miners

Geoffrey Berry, Graham W. Gibbs

PII: S0273-2300(07)00141-9
DOI: 10.1016/j.yrtph.2007.09.012
Reference: YRTPH 2057

To appear in: *Regulatory Toxicology and Pharmacology*

Received Date: 5 September 2007
Accepted Date: 30 September 2007

Please cite this article as: Berry, G., Gibbs, G.W., An Overview of the Risk of Lung Cancer in Relation to Exposure to Asbestos and of Taconite Miners, *Regulatory Toxicology and Pharmacology* (2007), doi: 10.1016/j.yrtph.2007.09.012

An Overview of the Risk of Lung Cancer in Relation to Exposure to Asbestos and of Taconite Miners

Geoffrey Berry[a,*], Ph.D. and Graham W. Gibbs, Ph.D.[b]

[a] *School of Public Health, University of Sydney, NSW 2006, Australia.*

[2 b] *Safety Health Environment International Consultants Corp., 38 Athabasca Avenue, Suite 101, Devon, Alberta, Canada*

* Corresponding author. Phone: +61 2 9924 2700, Fax: +61 2 9924 2700
E-mail address: gberrycons@optusnet.com.au (Geoffrey Berry)

Keywords: mesothelioma; amosite; grunerite; taconite; crocidolite; tremolite; anthophyllite; winchite; risk assessment, etiology

Abstract

Exposure-response relationships between the relative risk of lung cancer and quantitative measures of exposure to asbestos are available from a number of epidemiological studies. Meta-analyses of these relationships have been published by Lash *et al*. (1997) and Hodgson and Darnton (2000). In this paper the risks derived in these meta-analyses have been compared. Lash *et al*. concentrated on process and found that the risk of lung cancer increased as the asbestos is refined by processing. Hodgson and Darnton concentrated on fibre type and found that the risk was highest for exposure to amphibole asbestos (crocidolite and amosite), lowest for chrysotile and intermediate for mixed exposure. Some of the differences between the conclusions from the two meta-analyses are a consequence of the choice of studies included. The range of asbestos types included in the studies in the analysis of Hodgson and Darnton was wider than that in Lash *et al*., enabling differences between fibre types to be analyzed more readily. There are situations where occupational exposure to chrysotile asbestos has shown no detectable increase in risk of lung cancer. Taconite miners have shown no increased risk of mortality due to lung cancer.

Introduction

The association of lung cancer with exposure to asbestos has been beyond dispute for almost 50 years following the epidemiological study of asbestos textile workers reported by Doll (1955). In the following decades there have been many studies of particular situations reported, and in some quantitative data on exposure have been available allowing consideration of exposure-response relationships. The more recent work on quantitative exposure-response relationships has enabled risk estimates to be derived including estimates due to environmental exposure based on direct study in addition to extrapolation from occupational situations.

Meta-analyses and measures of effect

Meta-analyses of exposure-response relationships between the relative risk (RR) of lung cancer and cumulative exposure to asbestos (d) have been published by Lash *et al*. (1997) and by Hodgson and Darnton (2000). Lash *et al*. included 15 cohorts, and fitted the linear dose-response model within each cohort:

$$RR = A\,(1 + kd)$$

where A is an intercept term, that is the relative risk for zero exposure, k is the slope, or increase in relative risk per unit of exposure, and d is the cumulative exposure (fibres/ml years).

Hodgson and Darnton included 17 cohort studies in their analysis and fitted the average dose-response effect estimated for each cohort. They defined an average effect as

$$R_L = 100 * (SMR - 1) / X$$

where SMR is the ratio of observed to expected lung cancer deaths for the whole cohort, and X is the mean exposure (fibres/ml years) of the cohort. R_L is the percentage excess risk per unit of exposure and was taken as the slope of the relationship

$$RR = 1 + R_L d / 100.$$

The intercept, relative risk for zero exposure, was taken as 1.

The relationships used in the two meta-analyses were similar, but a difference was that since Lash *et al*. fitted exposure-response relationships within each study, they were able to estimate the intercept, as well as the slope, of the relationship. In contrast Hodgson and Darnton included studies where only the average exposure was available and thus were forced to assume that the intercept was unity in order to estimate the slope. Although this seems a reasonable choice, since zero exposure clearly gives no associated increase in risk, the intercept is not necessarily equal to unity because the reference population, from which death rates are taken for the calculation of expected deaths, may not correspond exactly to that of the workers in a study due to difference in other local factors or differences in smoking levels (Liddell and Hanley, 1985).

The relationship between the slopes used in the two meta-analyses is

$$R_L = 100\ k$$

Another way of expressing the slope is by its inverse which gives the cumulative exposure at which the relative risk is doubled

$$D\ (RR=2) = 100/R_L = 1/k$$

Lash *et al*. (1997) concentrated their analysis on process (Table 1) and concluded that the risk of lung cancer increases as the asbestos is refined by processing (mining/milling - cement products - textiles/manufacturing). They found that adding a multiplicative term for predominantly chrysotile use added no significant information. The estimate of the multiplicative term was 0.19 (95% confidence interval 0.02 to 1.6).

Hodgson and Darnton (2000) concentrated on fibre type (Table 2) and found the highest risk for the amphiboles, crocidolite and amosite, a much lower risk for chrysotile, and an intermediate risk for exposure to mixed amphibole and chrysotile.

Comparison of “Lash *et al.*” and “Hodgson and Darnton”

There were 11 studies in common to the two meta-analyses so that the values may be compared:

1. Paterson insulation factory processing amosite (Seidman *et al*. 1986);
2. Ontario asbestos cement plant using chrysotile and crocidolite (Finkelstein 1984);
3. Pennsylvania textile factory processing mainly chrysotile and amosite (McDonald *et al*. 1983);
4. Vöcklabruck asbestos cement factory using chrysotile and crocidolite (Neuberger and Kundi 1990);
5. Rochdale male textile factory workers processing mainly chrysotile but with some crocidolite (Peto *et al*, 1985);

6. Johns Manville retirees working in production or maintenance with mixed exposures to chrysotile, crocidolite and amosite (to 1980 Enterline *et al*, 1987; to 1973 Henderson and Enterline 1979);
7. New Orleans asbestos cement (plant 1) using mainly chrysotile, small amounts of amosite and later crocidolite irregularly (Hughes *et al*. 1987);
8. South Carolina male textile factory workers using chrysotile (Dement *et al*. 1994);
9. Connecticut friction products plant processing chrysotile (McDonald *et al*. 1984);
10. Quebec chrysotile miners and millers (to 1992, Liddell *et al*. 1997; to 1989, McDonald *et al*. 1993);
11. Balengero chrysotile miners (Piolatto *et al*. 1990).

The values of R_L from both meta-analyses are given in Table 3 and Figure 1. Excluding those studies with a zero value of R_L in either analysis, the range of values is of over two orders of magnitude. For six of the studies the two meta-analyses give fairly similar values. For Paterson (study 1) and Ontario (study 2), Hodgson and Darnton give a value about 7 times higher than Lash *et al*. For both of these studies Lash *et al*. estimated the value of A as over 3, that is they found a high rate of lung cancer for zero exposure. The opposite occurred for Pennsylvania (study 3), where Lash *et al.* give a value over four times higher than Hodgson and Darnton, and the value of A was only 0.5. For Connecticut (study 9) and Vöckalbruck (study 4), Hodgson and Darnton give moderate values of R_L whilst Lash *et al*. give zero. Again for both of these Lash *et al*. found a high lung cancer rate for zero exposure (1.6 and 2.1). For New Orleans (study 7) Hodgson and Darnton found no excess risk overall but Lash *et al*. found an exposure-response relationship within the study.

For the Ontario study there were only 21 lung cancer deaths and examination of the plot of the exposure-response data shows no clear pattern of effect. No reliable exposure-response relationship may be fitted (the 95% confidence interval given by Lash *et al*. for R_L is from 0 to 25) and it is not surprising that the two methods differ.

Some of the differences between the conclusions from the two meta-analyses are a consequence of the choice of studies included. Lash *et al*. included two mining populations, both chrysotile mining. Consequently once the industry was taken into account there was no possibility of finding a fibre type effect within this industry. In contrast Hodgson and Darnton included the two chrysotile mines but also crocidolite mines in Australia and South Africa, and an amosite mine in South Africa. Of the 19 sub-groups analysed by Hodgson and Darnton there were 3 with exposure to crocidolite, 2 to amosite, 5 to chrysotile, and 9 with mixed exposure to chrysotile and amphibole. Lash *et al*. included 15 cohorts but for two an exposure-response relationship could not be fitted and another was of a vermiculite mine with tremolite in the ore. Of the other 12, 1 involved exposure to amosite, 4 to chrysotile, and 7 mixed exposure to chrysotile and amphibole, of which 5 were predominantly to chrysotile. There was less variation in fibre type between the studies included by Lash *et al*., compared with those included by Hodgson and Darnton, and consequentially there was less opportunity to explore differences in effect between fibre types.

Chrysotile has been processed with no detectable increase in lung cancer, as shown by the study of workers manufacturing friction products at the Ferodo factory in the north of England (Table 4) (Newhouse and Sullivan, 1989).

Problems in estimating exposure

There are uncertainties in the measurements of exposure, arising from changes in instrumentation, problems in conversion of results obtained using old types of instruments to modern methods, a lack of systematic sampling in early years, and consequentially the use of “guestimates” of early exposure (Rogers, 2001). A consequence of this is that exposure-response relationships which may be qualitatively valid within a study because relative exposure levels are reasonable, can be invalid outside the study because absolute exposure levels are incorrect.

Taconite and cummingtonite-grunerite

A cohort study of miners at the Reserve Mining Company was reported by Higgins *et al*. (1983). 5751 workers employed for a year or more between 1952 and 1976 were followed up until 1976 (a maximum of 24 years). For all causes of death there were 298 deaths, compared with an expected number of 344 (SMR = 87). For mortality due to respiratory cancer, there were 15 observed deaths, compared with an expected number of 18 (SMR = 84). These include deaths soon after exposure, and after 15 years latency, there were 103 deaths (expected 115, SMR = 90) including 8 respiratory cancer deaths (expected 7.9, SMR = 102). There were no apparent exposure-response trends.

Another cohort study of Minnesota taconite miners and millers was reported by Cooper *et al*. (1988, 1992), in which the mortality experience of 3431 men employed for 3 months or more between 1947 and 1958 in either the Erie or Minntac operations was compared with both US and Minnesota white males death rates. The Minnesota death rates are less than the US rates for all causes and for respiratory cancer. The observed and expected mortality to 1983 and 1988 for deaths due to all causes and respiratory cancer, compared with expected numbers calculated using Minnesota rates, are shown in Table 5.

Mortality due to respiratory cancer was analysed by time since first exposure (Table 6). There was clearly no excess mortality due to respiratory cancer after a 10 year latency period.

Three studies of miners exposed to cummingtonite-grunerite at the Homestake mine in South Dakota have been reported. These studies overlap so that the results are not independent. The first study was of 440 men employed for at least 5 years underground by 1960 (Gillam *et al*., 1976). Observed mortality was compared with expected mortality calculated using the death rates for South Dakota. In the period 1960 to 1973, there were 71 deaths due to all causes (expected 53, SMR 134), and 10 deaths due to respiratory cancer (expected 2.7, SMR 370). Analysing mortality due to respiratory cancer with respect to time since first exposure, the SMR was greater in the first 20 years than later.

The second study was of 1321 men employed for at least 21 years by 1973 (McDonald *et al*., 1978). Expected deaths were calculated using South Dakota rates. Between 1937 and 1973, there had been 631 deaths (expected 550, SMR 115). For respiratory cancer there were 17 deaths (expected 16.5, SMR 103). The results were examined in terms of exposure-response relationships. Clear relationships were found for pneumoconiosis and respiratory tuberculosis, but not for respiratory cancer.

The third study was 3328 men employed underground for at least a year during 1940 to 1964 (Brown *et al*., 1986). Deaths occurring in the period 1941 to 1977 were analysed, with expected deaths calculated using US rates. There were 861 from all causes (expected 769, SMR 112). After 15 years latency there were 41 deaths due to lung cancer (expected 40, SMR 102). Restricting this analysis to those with 10 or more years of exposure there were 21 deaths due to lung cancer (expected 18.2, SMR 115).

Taking all these studies there is no convincing evidence of an increase in deaths due to lung cancer in the Homestake miners. The excess reported by Gillam *et al*. (1976) is not supported by the other two studies, and attributing this excess to the exposure in the mine is questionable given that the relative risk was higher within the first 20 years since first exposure than later. The results have been reviewed by Ross *et al*. (1993).

Environmental exposure

Camus *et al*. (1998) reported a study of women living in two chrysotile asbestos mining areas in Quebec, over the period 1970 to 1989. The average cumulative exposure was estimated as 25 fibres/ml years, with a plausible range from 5 to 125 fibres/ml years, equivalent to 105 fibres/ml working yrs, after converting to the measure used for occupational exposure over 40 hours a week.

There had been 71 deaths due to lung cancer, compared with 71.4 expected from rates in unexposed areas. Predictions based on an EPA model (RR = 1 + 0.01 cumexp) gave a relative risk of 2.05 and 146 lung cancer deaths (excess of 75). Clearly the EPA model was inappropriate. Using the risk estimate for Quebec mining and milling from Hodgson and Darnton (RR = 1 + 0.0006 cumexp) gives a relative risk of 1.06 predicting 76 lung cancer deaths (excess of 5). The risk estimate for this industry from Lash *et al*. is RR = 1+0.00025cumexp) which gives a relative risk of 1.025 predicting 73 lung cancer deaths (excess of 2). Thus, both these estimates are in accord with the observed number of 71 when taking account of chance variation. However, for such a low relative risk whether there is any actual excess or not is not detectable.

Risk at low exposure

A linear dose-response relationship between relative risk of lung cancer and exposure is often used ("a widely accepted and scientifically reasonable compromise rather than an established scientific principle" (HEI, 1991)). Non-linearity and/or the existence of a threshold at low levels of exposure are very difficult, perhaps impossible, to detect from epidemiological data (Liddell, 2001). Depending on the potency of the agent low exposures can result in risks that are so low that they are undetectable from epidemiological studies.

Summary

Asbestos exposure increases lung cancer incidence. There are situations where occupational exposure to chrysotile asbestos has shown no detectable increase in risk. Taconite miners have shown no increased risk of mortality due to lung cancer.

References

Brown, D.P., Kaplan, S.D., Zumwalde, R.D., Kaplowitz, M., and Archer, V.E. (1986). Retrospective cohort mortality study of underground gold mine workers. In *Silica, Silicosis, and Cancer* (D.F. Goldsmith, D.M. Winn, and C.M. Shy Eds.) pp 335-350. Praeger, New York.

Camus, M., Siemiatycki, J., and Meek, B. (1998). Nonoccupational exposure to chrysotile asbestos and the risk of lung cancer. *N. Engl. J. Med.* **338**, 1565-71.

Cooper, W.C., Wong, O., and Graebner, R. (1988). Mortality of workers in two Minnesota taconite mining and milling operations. *J. Occup. Med.* **30**, 506-511.

Cooper, W.C., Wong, O., Trent, L.S., and Harris, F. (1992). An updated study of taconite miners and millers exposed to silica and non-asbestiform amphiboles. *J. Occup. Med.* **34**, 1173-1180.

Dement, J.M., Brown, D.P., and Okun, A. (1994). Follow-up study of chrysotile asbestos textile workers: cohort mortality and case-control analyses. *Am. J. Ind. Med.*, **26**, 431-447.

Doll R. (1955). Mortality from lung cancer in asbestos workers. *Br. J. Ind. Med.* **12**, 81-86.

Enterline, P.E., Hartley, J., and Henderson, V. (1987). Asbestos and cancer: a cohort followed up to death. *Br. J. Ind. Med.*, **44**, 396-401.

Finkelstein, M. M. (1984). Mortality among employees of an Ontario asbestos-cement factory. *Am. Rev. Respir. Dis.* **129**, 754-761.

Gillam, J.D., Dement, J.M., Lemen, R.A., Wagoner, J.K., Archer, V.E., and Blejer. H.P. (1976). Mortality patterns among hard rock gold miners exposed to an asbestiform mineral. *Ann. N. Y. Acad. Sci.* **271**, 336-344.

HEI, 1991

Henderson, V.L., and Enterline, P.E. (1979). Asbestos exposure: factors associated with excess cancer and respiratory disease mortality. *Ann. N.Y. Acad. Sci.*, **330**, 117-126.

Higgins, I.T.T., Glassman, J.H., Oh, M.S., and Cornell, R.G. (1983). Mortality of Reserve Mining Company employees in relation to taconite dust exposure. *Am. J. Epidem.* **118**, 710-719.

Hodgson, J.T., and Darnton, A. (2000). The quantitative risks of mesothelioma and lung cancer in relation to asbestos exposure. *Ann. Occup. Hyg.* **44**, 565-601.

Hughes, J.M., Weill, H., and Hammad, Y.Y. (1987). Mortality of workers employed in two asbestos cement manufacturing plants. *Br. J. Ind. Med.*, **44**, 161-174.

Lash, T.L., Crouch, E.A.C., and Green, L.C. (1997). A meta-analysis of the relation between cumulative exposure to asbestos and relative risk of lung cancer. *Occup. Environ. Med.* **54**, 254-263.

Liddell, D. (2001). The quantitative risks of mesothelioma and lung cancer in relation to asbestos exposure (letter to editor). *Ann. Occup. Hyg.* **45**, 329-335.

Liddell, F.D.K., and Hanley, J.A. (1985). Relations between asbestos exposure and lung cancer SMRs in occupational cohort studies. *Br. J. Ind. Med.* **42**, 389-396.

Liddell, F.D.K., McDonald, A.D., and McDonald, J.C. (1997). The 1891-1920 cohort of Quebec chrysotile miners and millers: development form 1904 and mortality to 1992. *Ann. Occup. Hyg.*, **41**, 13-36.

McDonald, A.D., Fry, J.S., Woolley, A.J., and McDonald, J.C. (1983). Dust exposure and mortality in an American factory using chrysotile, amosite, and crocidolite in mainly textile manufacture. *Br. J. Ind. Med.* **40**, 368-374.

McDonald, A.D., Fry, J.S., Woolley, A.J., and McDonald, J.C. (1984). Dust exposure and mortality in an American chrysotile asbestos friction products plant. *Br. J. Ind. Med.* **41**, 151-157.

McDonald, J.C., Gibbs, G.W., Liddell, F.D.K., and McDonald, A.D. (1978). Mortality after long exposure to cummington-grunerite. *Am. Rev. Respir. Dis.* **118**, 271-277.

McDonald, J.C., Liddell, F.D.K., Dufresne, A., and McDonald, A.D. (1993). The 1891-1920 birth cohort of Quebec chrysotile miners and millers: mortality 1976-88. *Br. J. Ind. Med.* **50**, 1073-1081.

Neuberger, M., and Kundi, M. (1990). Individual asbestos exposure: smoking and mortality – a cohort study in the asbestos cement industry. *Br. J. Ind. Med.*, **47**, 615-620.

Newhouse, M.L., and Sullivan, K.R. (1989). A mortality study of workers manufacturing friction materials: 1941-86. *Br. J. Ind. Med.* **46**, 176-179.

Peto, J., Doll, R., Hermon, C., Binns, W., Clayton, R., and Goffe, T. (1995). Relationship of mortality to measures of environmental asbestos pollution in an asbestos textile factory. *Ann. Occup. Hyg.* **29**, 305-355.

Piolatto, G., Negri, E., La Vecchia, C., Pira, E., Decarli, A., and Peto, J. (1990). An update of cancer mortality among chrysotile asbestos miners in Balangero, northern Italy. *Brit. J. Ind. Med.* **47**, 810-814.

Rogers A. (2001). *An evaluation of the exposure criteria and lung fibre burden associated with the Helsinki Criteria and its applicability to Australia.* Dust Diseases Board of New South Wales Research Report, November 2001.

Ross, M., Nolan, R.P., Langer, A.M., and Cooper, W.C. (1993). Health effects of mineral dusts other than asbestos. In *Health Effects of Mineral Dusts* (G. Guthrie, and B.T. Mossman Eds.) pp. 361-407. Mineralogical Society of America, Washington, D.C.

Seidman, H., Selikoff, I.J., and Gelb, S.K. (1986). Mortality experience of amosite asbestos factory workers: dose-response relationships 5 to 40 years after onset of short-term work exposure. *Am. J. Ind. Med.* **10**, 479-514.

Table 1 Estimates of k (increase in relative risk per fibre/ml year of exposure) by industry from the meta-analysis of Lash *et al*. (1997)

	k	D(RR =2)
All studies	0.0026	385
Mining and milling	0.00025	4000
Cement products	0.0034	294
Manufacturing/textiles	0.0077	130

Table 2 Values of R_L (the percentage excess risk per fibre/ml year of exposure) by fibre type from the meta-analysis of Hodgson and Darnton (2000)

	R_L	D(RR =2)
Crocidolite	4.2	24
Amosite	5.2	19
Mixed (amphibole/chrysotile)	0.47	213
Chrysotile	0.062	1613

Table 3 Values of R_L (the percentage excess risk per fibre/ml year of exposure) from the meta-analyses of Hodgson and Darnton and Lash *et al*. for the 11 cohort studies in common to the two analyses

		Value of R_L	
		H&D	Lash *et al*.
1	Paterson insulation factory	5.8	0.88
2	Ontario asbestos cement plant	5.2	0.69
3	Pennsylvania textile factory	0.8	3.6
4	Vöcklabruck asbestos cement factory	0.45	0
5	Rochdale textile factory (men)	0.37	0.41
6	Johns Manville retirees	0.21	0.25
7	New Orleans asbestos cement (plant 1)	0	0.066
8	South Carolina textile factory (men)	4.6	2.4
9	Connecticut friction products plant	0.8	0
10	Quebec chrysotile miners and millers	0.06	0.02
11	Balengero chrysotile miners	0.03	0.02

Table 4 Mortality due to lung cancer at Ferodo friction products factory (Newhouse and Sullivan, 1989)

	Lung cancer deaths		
	Observed	Expected	SMR
Men	229	221.4	103
Women	12	21.1	57
Total	241	242.5	99

Table 5 Mortality of taconite miners and millers at the Erie and Minntac operations in Minnesota, compared with Minnesota death rates (Cooper *et al*., 1988, 1992)

	All causes			Respiratory cancer		
	obs	exp	SMR	obs	exp	SMR
To 1983	801	820	98	41	48	85
To 1988	1058	1165	91	65	67	97

Table 6 Mortality due to respiratory cancer of taconite miners and millers at the Erie and Minntac operations in Minnesota, compared with Minnesota death rates by time since first exposure (Cooper *et al*. 1992)

Time since first exposure	obs	SMR
- 10 yr	7	145
10-19 yr	12	75
20+ yr	46	99

Figure 1 Values of R_L (the percentage excess risk per fibre/ml year of exposure) from the meta-analyses of Hodgson and Darnton and Lash *et al*. for the 11 cohort studies in common to the two analyses. The points are labelled by the study number (text and Table 3). (To facilitate plotting on the log scales, the three zero values have been plotted at 0.002).